REMARKS/ARGUMENTS

In response to the Final Office Action of December 14, 2006, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claim 1 has been allowed. Claims 36-43 have been cancelled. Claims 2-35 were cancelled in a previous Response filed on June 13, 2003. New claims 44-50 have been added. Claims 1 and 44-50 are under examination and remain pending in the instant application.

No new matter has been added by the addition of new claims 44-50. New claims 44-50 find basis in previously presented claims 36-43, now cancelled.

Claim 44 clarifies that the claimed method involves identification of a peptide in a sample by comparison of mass spectral patterns, *i.e.* comparison of a known mass spectral profile to experimentally-derived mass spectral profiles. The steps used to prepare a sample for analysis by mass spectrometry are disclosed in detail in the instant specification as originally filed; page 12, lines 2-6 and page 20, line 7 to page 25, line 15. The steps of the mass spectrometric analysis (SELDI and tandem) are disclosed in detail in the instant specification as originally filed; page 25,

line 10 to page 27, line 16. The characteristic profile of the claimed peptide is shown in Figure 2, *i.e.* a known profile.

Claim 46 clarifies that peptides can be analyzed by SELDI and/or tandem mass spectrometric techniques; see the instant specification as originally filed at page 20, lines 2-6 and page 27, lines 6-16. In the original experiments in which the claimed peptide was identified, peptides were analyzed by both SELDI and tandem mass spectrometry.

Claims 48-50 clarify that the claimed kit is used for determining presence of the known peptide, amino acid residues 2-12 of SEQ ID NO:1 as disclosed herein, in an unknown sample; see the instant specification as originally filed at page 28, line 3 to page 29, line 7.

* Please note that the Examiner's comments from the Office Action, as reiterated herein, are single spaced to clearly delineate the Examiner's comments from Applicants' comments.

Rejection under 35 USC 112, first paragraph

Claims 36-43, as presented on September 18, 2006, stand rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner asserts that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands* (8USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f)the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

The Examiner asserts in considering the factors for the instant claims:

a) In order to use the claimed invention one of skill in the art must identify a specific amino acid sequence from a mass spectrometry peak that relates only the mass to charge ratio. For the reasons discussed below, there would be an unpredictable amount of experimentation required to practice the claimed invention.

b) The description does not provide detailed guidance as to how to confirm a specific amino acid sequence with a mass spectrometry peak that only provides mass to charge ratio information.

c) The description does not provide working examples of confirming a specific amino acid sequence from a mass spectrometry peak.

d) The nature of the invention, of confirming a specific polypeptide sequence required knowledge of specific ordering of amino acids in the sequence.

e) The prior art shows that mass spectrometry can give information of the mass to charge ratio of polypeptide fragments, however, determining the exact sequence from a single mass spectrometry peak is not taught.

f) The skill of those in the art of polypeptide sequence characterization is high.

g) The predictability of the relationship of connection of the location of a single mass spectrometry peak (i.e. the polypeptide mass) to the exact sequence that confirms a specific polypeptide is unknown in the prior art.

h) The claims are broad in that they do not specify how an exact polypeptide sequence can be confirmed from only a single mass spectrometry peak.

The Examiner asserts that the skilled practitioner would first turn to the instant description for guidance in using the claimed invention. However, the description lacks clear evidence that a specific sequence of amino acids in a particular order can be determined from a single mass spectrometry peak. As such, the skilled practitioner would turn to the prior art for such guidance, however the prior art does not discuss the determination of amino

acid arrangements from one mass spectrometry peak. Finally, said practitioner would turn to trial and error experimentation to confirm the polypeptide sequence claimed. The Examiner concludes that such amounts to undue experimentation.

The Examiner asserts that claim 36 (c) recites "confirming the presence of... amino acid residues 2-12 of SEQ ID NO:1 in said sample by identifying a mass spectral profile having an ion peak at about 1348 daltons . . ." The mass spectrometry peak at 1348 daltons (or about 1348) is used to confirm the presence of the specific polypeptide with the sequence disclosed and described on page 31, lines 13-16 of the specification. However, the use of the mass spectrometry peak at "about 1348 daltons" for the confirming of said sequence is not enabled because a sequence with same amino acids but in a different order of arrangement would also be detected at 1348 daltons. Additionally, a similar amino acid sequence with slight modifications could also potentially have a mass of "about 1348 daltons". Therefore, the Examiner concludes that the identification of the peak does not confirm the presence of the claimed sequence in the sample.

Reply to Applicants

The Examiner asserts that Applicants' arguments filed 9/18/2006 have been fully considered but not found persuasive.

Applicants' argue that diagnosis of myocardial infarction, intracerebral hemorrhage, or congestive heart failure is made if the mass spectral profile as shown in Figure 2 is found in a mass spectral profile obtained from an unknown sample when the claimed peptide (amino acid residues 2-12 of SEQ ID NO:1) is determined to be present in the sample and the patient from which the sample is obtained is diagnosed with myocardial infarction, intracerebral hemorrhage, or congestive heart failure (Remarks, page 11, lines 10-18).

The Examiner asserts that the features upon which applicant relies (*i.e.*, Remarks, page 11, lines 10-18) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Claim 36 recites that the identification of a peak at 1348 daltons with mass spectrometry confirms the presence of a biopolymer marker consisting of amino acid residues 2-12 of SEQ ID NO:1 and diagnoses myocardial infarction, intracerebral hemorrhage, or congestive heart failure (claim 36, part (c)). The claims do not recite any previous or additional diagnosis of the patient as argued by Applicant (Remarks, page 11, lines 16-18)

which is needed to diagnose the patient using the identification of the marker.

Furthermore, the Examiner asserts that mass spectrometry alone is not sufficient to determine the absolute presence of the recited sequence. The specification recites further tests to discern the presence of the sequence (Specification, page 26, line 20, to page 27, line 2). The presence of each marker specific to the disease is also tested (Specification page 28, lines 17-20).

Applicants respectfully disagree with all of the Examiner's assertions.

Claims 36-43 have been cancelled. New claims 44-50 incorporate the subject matter of cancelled claims 36-43.

The Examiner asserts that the description lacks clear evidence that a specific sequence of amino acids in a particular order can be determined from a single mass spectrometry peak.

However, Applicants respectfully submit that a method requiring identification of a specific sequence of amino acids in a particular order from a single mass spectrometry peak is not claimed.

The identification of the described peptide (amino acid residues 2-12 of SEQ ID NO:1) in a sample is determined by matching a mass spectral profile, not an amino acid sequence.

The instant specification discloses both a novel peptide marker (amino acid residues 2-12 of SEQ ID NO:1) and methods for using this marker. The specification describes how the claimed peptide marker was identified: a sample was obtained from a patient, submitted to chromatography in preparation for mass spectrometry, analyzed by SELDI mass spectrometry and sequenced by

tandem mass spectrometry (page 12, lines 2-6; page 20, line 7 to page 25, line 15 and page 25, line 10 to page 27, line 16). Furthermore, several uses for the identified peptide were contemplated in the instant specification (page 17, lines 3-6; page 18, lines 5-7 and page 28, line 3 to page 33, line 2); for example, tests for determining the presence of the identified peptide marker in samples, wherein presence indicates a positive correlation with myocardial infarction, intracerebral hemorrhage or congestive heart failure.

The instant specification provides a mass spectral profile characteristic of the claimed biopolymer marker; see Figure 2. Mass spectral profiles are reproducible; many have been published and/or stored in databases for reference purposes. The mass spectral profile shown in Figure 2 is a reference mass spectral profile. This mass spectral profile can be compared with mass spectral profiles obtained from unknown samples. If the pattern of this reference mass spectral profile, *i.e.* an ion peak at about 1348 daltons, matches to a pattern found in a mass spectral profile from an unknown sample, then the claimed peptide marker (amino acid residues 2-12 of SEQ ID NO:1) is determined to be present in the unknown sample and thus indicative of myocardial infarction, intracerebral hemorrhage or congestive heart failure. Thus, contrary to the Examiner's assertion, neither the specification nor

the claims involve identifying specific amino acid sequences from a single mass spectral peak.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? MPEP 2164.01

In the instant case, any skilled artisan could utilize the mass spectral profile provided in the specification (Figure 2) as a reference for comparing with mass spectral profiles of peptides obtained from unknown samples to determine the presence of the claimed peptide marker (amino acid residues 2-12 of SEQ ID NO:1) as the mass spectral profile provided in the specification is the characteristic profile of the claimed marker peptide. The only experimentation required would be to obtain a sample from a patient and analyze the sample by mass spectrometry. Such procedures are commonly practiced and could be accomplished within a short period of time. If mass spectral profiles match, the identified peptide is present in the sample and thus indicative of myocardial infarction, intracerebral hemorrhage or congestive heart failure. Thus, Applicants respectfully submit that the experimentation needed to practice the invention is neither undue nor unreasonable.

An applicant may cite references to show what one skilled in the art knew at the time of filing the application. MPEP 2164.05 The utilization of mass spectral peaks for identification of biomarkers was known and in practice at the time that the instant application was filed. For example, Lynn et al. (Rapid Commun Mass Spectrum 13(20):2022-2027 1999; abstract attached hereto, labeled as reference #1) disclose reproducible mass spectral peaks that can be used as biomarkers to distinguish between species of bacteria. Thus, Applicants respectfully submit that one of ordinary skill in the art would have known at the time that the instant application was filed that mass spectral profiles are useful reference tools.

The Examiner asserts that the claims do not recite any previous or additional diagnosis of the patient as argued by Applicant (Remarks, page 11, lines 16-18) which is needed to diagnose the patient using the identification of the marker.

Applicants respectfully submit that "previous or additional diagnosis" is not required. This passage of the Remarks (page 11, lines 16-18) simply refers to the use of the mass spectral profile (shown in Figure 2) as a reference to determine the presence of the claimed peptide marker (amino acid residues 2-12 of SEQ ID NO:1) in unknown samples.

Furthermore, the Examiner asserts that the specification recites further tests to discern the presence of the sequence (Specification, page 26, line 20, to page 27, line 2). The presence of each marker specific to the disease is also tested (Specification page 28, lines 17-20).

The specification at page 26, line 20 to page 27, line 2 refers to the observation of the results of mass spectrometric analysis to discern whether or not the peptides identified are useful markers, for example, as described herein, a useful marker is present in a disease state and absent in a normal, healthy state. This type of analysis is also discussed in the specification at page 5, lines 7-14.

The specification at page 28, lines 17-20 refers to methods that were contemplated for use after the disease-specific marker was identified, *i.e.* methods for using the identified peptide marker not methods to identify the peptide marker. In other words, the specification discloses a marker and then discloses how it can be used. This can be ascertained from the paragraph at page 28, lines 3-10, which states, "In accordance with various stated objectives of the invention, the skilled artisan, in possession of the specific disease-specific marker as instantly disclosed. . . " Emphasis added by Applicants.

Based upon all of the above arguments, Applicants assert that an artisan of ordinary skill, when reviewing the instant specification and given the high level of knowledge and skill in the art, would know how to use the mass spectral profile of the claimed marker peptide, as shown in Figure 2, as a reference to

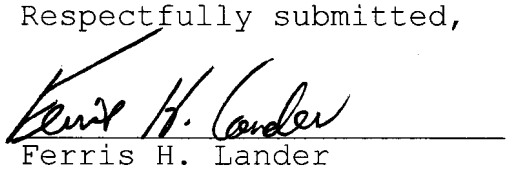
identify the marker in unknown samples. Accordingly, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

The Commissioner for Patents is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayments in any fees paid on the filing to Deposit Account No. 50-1803.

Respectfully submitted,



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1: Rapid Commun Mass Spectrom. 1999;13(20):2022-7.

Identification of Enterobacteriaceae bacteria by direct matrix-assisted laser desorptiom/ionization mass spectrometric analysis of whole cells.

Lynn EC, Chung MC, Tsai WC, Han CC.

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Several members of Enterobacteriaceas were analyzed by matrix-assisted laser desorption ionization (MALDI) time-of-flight mass spectrometry (TOFMS). Characteristic mass spectral peaks and patterns were observed in the mass range of 2 to 20 kDa. The mass peaks reported to be reproducibly observed by previous researchers, which were claimed to serve as species/strain-specific biomarkers, are consistently observed in our current study. Despite the high degree of similarity found in the MALDI mass spectra within the enteric bacteria, minor yet notable differences existed to allow their differentiation. Five spectral peaks at m/z 4364, 5380, 6384, 6856, and 9540, generated reproducibly for each genus studied here, are assigned as family-specific biomarkers for the Family Enterobacteriaceae. The mass peaks at m/z 7324, 7724, 9136, and 9253 are assigned as genus-specific biomarkers for Salmonella. Some unique biomarkers characterizing the species and strains of E. coli are also presented. Copyright 1999 John Wiley & Sons, Ltd.

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